

## REMARKS

Applicants have restored, as required in the Notice of Non-Compliant Amendment, the contents of Claims 7 and 10, which have been withdrawn by the Examiner in an Office Action of December 5, 2008, and, for the convenience of the Examiner, have included all Claims and Remarks, with some minor amendments, from their Response of April 6, 2009, except for the inclusion of a Supplemental Information Disclosure Statement and two non-patent references assumed still available to the Patent Office from Applicants' April 6 Response.

Applicants appreciatively acknowledge the telephone interviews with Examiner Samantha Shterengarts on Monday, March 30, 2009, during which Applicants' Attorney was requesting Examiner Shterengarts' advice on handling some apparent inconsistencies between the Claims submitted in their Preliminary Amendment filed July 19, 2006, and stamped by the United States Patent Office on July 19, 2006, and the amended Claims submitted with their Response to Restriction Requirement filed November 7, 2008, on which the Examiner based her Actions. Applicants very much appreciate that she consulted with two USPTO supervisors and suggested how Applicants' Attorney should deal with some of those possible inconsistencies. Some of the following amendments reflect her advice, as interpreted in good faith by Applicants' Attorney.

Claim 1 has been amended by limiting the definitions of substituents on the compound of formula I and with minor stylistic changes.

Claim 2 has been amended consistent with the amendments to Claim 1, and with additional minor grammatical and stylistic changes.

Claim 3 has been amended by the substitution of "and" for "or", as is correct grammatical and Markush series usage, and with other minor grammatical or stylistic changes for clarity.

Claims 4 and 8 have been amended, in addition to the deletions made in the Preliminary

Amendment, with minor stylistic or grammatical changes.

The cancellation of Claims 5 and 6, as originally included in the Preliminary Amendment, has been confirmed.

Claims 7 and 10 have been withdrawn by the Examiner as a result of Applicants' election, with traverse, of November 7, 2008, to initially prosecute the Claims of Group I, Claims 1-5, 8 and 9 in response to the Examiner's Restriction Requirement of September 8, 2008, now final.

Claim 9 has been amended, in addition to the deletions made in the Preliminary Amendment, by deletion of a redundant reference to Claim 2 as the source for the definition of R, with additional minor grammatical and stylistic changes.

No new matter has been added to the Application as a result of these amendments, or any of the amendments carried forward from the Preliminary Amendment, with Applicants retaining the right to deal with all canceled, deleted and/or withdrawn material in the future.

Claims 1-4 and 7-10 are currently pending in the instant Application, with Claims 7 and 10 withdrawn by the Examiner.

Applicants gratefully acknowledge the Examiner's indication that the compound of Example 1, which Applicants elected for search purposes in their Response of November 7, 2008, is patentable, and, in view of their amendments and arguments contained herein, respectfully request a favorable reconsideration of the entire pending Application.

The Examiner has indicated that Applicants' Information Disclosure Statement complied with the provisions of 37CFR1.97, but failed to comply with 37CFR1.98(a)(2) by failing to provide a legible copy of each non-patent literature publication.

~~Applicants have submitted herewith a copy of a Supplemental Information Disclosure Statement, listing the two references apparently not considered as a result of their previous submission, and have included copies of these two non-patent references.~~

Claims 3-5 and 8 have been objected to due to a lack of “and” in Claim 3, the use of “claim” rather than “claims” in Claims 4, 5 and 8, and “thereof” rather than “therefor” in Claim 5.

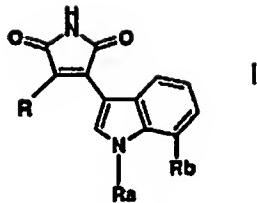
Applicants believe that their amendment to Claim 3 herein, and carrying forward of their removal of multiple dependencies from Claims 4 and 8 and cancellation of Claim 5, which had been included in the Preliminary Amendment, overcomes this objection. They respectfully request the Examiner’s reconsideration and removal of this objection.

Claims 1, 2, 4, 5 and 8 have been rejected under 35USC112, first paragraph, as constituents  $R_a$  and  $R_2$  are defined more broadly in the Claims than in the embodiments within the Specification.

Applicants believe that the definitions of  $R_a$  and  $R_2$  are clearly supported in paragraph [0002] on page 1, as well as by other supporting material and Examples in the Specification of the published version of their Application, and, therefore, respectfully request that this rejection be reconsidered and removed.

Claims 1, 2, 4, 5 and 8 have been rejected under 35USC103(a) as unpatentable over Evenou *et al* (WO 03/082859) and Albert *et al* (US2003/0069424).

Published International Application WO03/082859A1 (Novartis, with J-P. Evenou the first named inventor, “the ‘859 reference”) describes indolylmaleimide derivatives of



the formula , wherein  $R_a$  is H,  $CH_3$ ,  $CH_2-CH_3$  or isopropyl;  $R_b$  is H, halogen,  $C_{1-6}$ -alkoxy or  $C_{1-6}$ -alkyl; and R is one of five substituted radicals, in free form or pharmaceutically-acceptable salt form, which are useful in the prevention and/or treatment of diseases or disorders mediated by T-lymphocytes and/or PKC, e.g.,  $\alpha$ ,  $\beta$ ,  $\delta$ ,  $\epsilon$ ,  $\eta$ , or  $\theta$ , or GSK-3 $\beta$ , e.g., acute or chronic rejection of organ or tissue allo- or xenografts, graft-versus-host diseases, atherosclerosis, vascular occlusion due to vascular injury, such as angioplasty, restenosis, obesity, syndrome X, impaired glucose tolerance, polycystic ovary syndrome, hypertension, heart failure, chronic obstructive pulmonary disease, CNS diseases, such as Alzheimer's disease or amyotrophic lateral sclerosis, cancer, infectious diseases, such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury, e.g., myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock, e.g., traumatic brain injury, or T-cell-mediated acute or chronic inflammatory diseases or disorders or autoimmune diseases, e.g., rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes type I or type II and the disorders associated therewith, e.g., angiopathy, diabetic proliferative retinopathy, diabetic macular edema, nephropathy, neuropathy and dgn phenomenon, respiratory diseases, such as asthma or inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases, such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, inflammatory eye diseases, e.g., Sjögren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

6,645,970B2 (Albert *et al.*), "the '424 reference"] describes indolylmaleimide derivatives comprising either a substituted phenyl, naphthyl, tetrahydronaphthyl, quinazolinyl, quinolyl, isoquinolyl or pyrimidinyl residue useful in the treatment and/or prevention of T-cell-mediated acute or chronic inflammatory diseases or disorders, autoimmune diseases, graft rejection or cancer. Processes for preparation of these compounds and pharmaceutical compositions containing them are also described.

In the '859 reference, the moieties that would correspond to R<sub>1</sub> in Applicants' compounds are only in the 3-position of the naphthyl ring (viz, Examples 20-28), as well as on other rings in the other Examples. This represents more than simply a different substitution position from that in Applicants' compounds, as the distance of the R<sub>1</sub> moiety  $-(\text{CH}_2)_n-\text{NR}_3\text{R}_4$  is now not three carbon atoms (C=CH-C), but five carbon atoms (C-C=CH=CH-C)- an  $\alpha,\epsilon$  instead of an  $\alpha,\gamma$  binding- from the binding point of the naphthyl ring, leading to a substantially different structure from that of Applicants' compounds. Substituting in the '859 compounds an H in position 6 with  $-(\text{CH}_2)_n-\text{NR}_3\text{R}_4$  and the substituent in the '859 compounds' 3 position with a hydrogen is neither taught nor fairly suggested, and there is certainly no guidance as to the synthesis of naphthyl moieties with these different substitutions. These differences are very unlike changing the position of a small substituent, e.g., Cl, making the positional isomerism very complex, not at all a simple positional isomerism. Also, only heterocyclic rings are present at the 3 position in the reference, while Applicants' compounds comprise  $-(\text{CH}_2)_n-\text{NR}_3\text{R}_4$  moieties, where R<sub>3</sub> and R<sub>4</sub> are, independently, only hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl.

The '424 reference also teaches only compounds wherein NR<sub>16</sub>R<sub>17</sub> therein is in the 3 position of the naphthyl and all other rings shown, and exemplifies only nitrogen-containing rings in that position, or substitutents bound via an additional nitrogen or oxygen corresponding to X in  $-\text{X}-(\text{CH}_2)_n-\text{NR}_3\text{R}_4$ .

Clearly neither reference alone, nor any combination of these references, in any way teaches, suggests or provides any motivation for creating the novel and unobvious compounds of the instant invention.

Reconsideration and removal of this rejection is respectfully requested.

Claims 1, 2, 4, 5 and 8 have been rejected under 35USC103(a) as unpatentable over Davis *et al* (*J.Med.Chem.*, 35 (1), 1992, 177-184).

*J.Med.Chem.*, 1992, vol. 35 (1), pp. 177-184 (P.D.Davis *et al*) describes the role of protein kinase C<sup>2</sup> (PKC) and the therapeutic potential for inhibiting PKC for rheumatoid arthritis, cancer and AIDS, and the authors' search for and speculations on effective PKC inhibitors. The preparation of a number of different maleimides is described and the contributions of various features to the properties of the compounds is assessed, but they did not identify any compound to be a more potent PKC inhibitor than staurosporine.

In the Davis *et al* publication, only unsubstituted naphthyl moieties are included in Table III, and no moieties remotely resembling -(CH<sub>2</sub>)<sub>n</sub>-NR<sub>3</sub>R<sub>4</sub> are ever suggested. The pure amino (NH<sub>2</sub>) substituent of Examples 68 and 69 of the publication do not fall within Applicants' compounds, and the phenyl ring in Table V does not allow for the moiety in position 6 of Applicants' compounds. Finally, as the 4-substituted molecule of Example 63 demonstrates a lower inhibition than that of the similar 3-substituted compound of Example 69, it would be improbable that a skilled practitioner would believe or pursue substitutions at other than the 3 position as interesting.

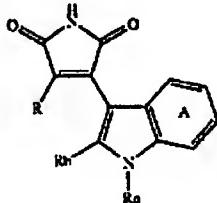
Clearly, an amino-substituted naphthyl at the 6 position would not be deducible from an unsubstituted naphthyl and the publication's amino-substituted phenyl, and therefore, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1, 2, 4, 5 and 8 have been provisionally rejected on nonstatutory obviousness-type double patenting grounds as unpatentable over Claims 12-15 and 18 of copending US Serial No. 11/708,840 [US2007/0155817A1 (Albert *et al*), a division of Application 10/660,442, now U.S.Patent 7,220,774, which is a continuation of U.S.Application 10/007,368, published as US2003/0069424A1, now U.S.Patent 6,645,970] and Claims 5, 6 and 8 of copending US Serial No. 10/586,421 [US2008/0242675A1 (Van Eis *et al*), which claims priority through a PCT Application, filed on the same day as the PCT Application from which the instant Application is the National Stage entry, to the same foreign priority filings as the instant Application].

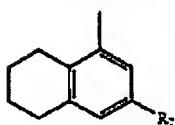
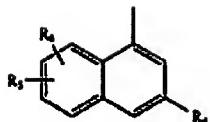
As neither this Application nor either of the cited Applications has been allowed, Applicants respectfully request the Examiner's forbearance until this Application and, separately, each of the other Applications has been conditionally allowed, at which time Applicants will take the appropriate action(s).

Claims 1, 2, 4, 5 and 8 have been rejected on nonstatutory obviousness-type double patenting grounds as unpatentable over Claims 1 and 9(??) of US Patent 7,220,774 and Claim 4 of US Patent 7,358,253.

United States Patent 7,220,774B2 (Albert *et al*), a continuation of U.S. Application 10/007,368, published as US2003/0069424A1, is directed to a compound of the formula

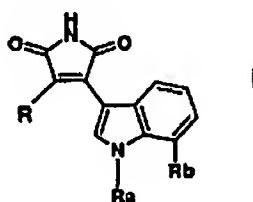


, wherein Ra is H, C<sub>1-4</sub>-alkyl or C<sub>1-4</sub>-alkyl substituted by OH, NH<sub>2</sub>, NHC<sub>1-4</sub>-alkyl or N(C<sub>1-4</sub>-alkyl)<sub>2</sub>; Rb is H or C<sub>1-4</sub>-alkyl; and R is a radical of one of the



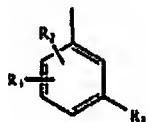
formulas , where each of R<sub>4</sub> and R<sub>7</sub> is OH, SH, NR<sub>16</sub>R<sub>17</sub>, wherein each of R<sub>16</sub> and R<sub>17</sub>, independently, is H or C<sub>1-4</sub>-alkyl or a radical of the formula -X-R<sub>c</sub>-Y, where X is a direct bond, O, S or NR<sub>18</sub>, wherein R<sub>18</sub> is H or C<sub>1-4</sub>-alkyl; R<sub>c</sub> is C<sub>1-4</sub>-alkylene or C<sub>1-4</sub>-alkylene, where one CH<sub>2</sub> is replaced by CR<sub>x</sub>R<sub>y</sub>, wherein one of R<sub>x</sub> and R<sub>y</sub> is H and the other is CH<sub>3</sub>, each of R<sub>x</sub> and R<sub>y</sub> is CH<sub>3</sub> or R<sub>x</sub> and R<sub>y</sub> together form -CH<sub>2</sub>-CH<sub>2</sub>-, and Y is bound to the terminal carbon atom and is selected from OH and -NR<sub>19</sub>R<sub>20</sub>, where each of R<sub>19</sub> and R<sub>20</sub>, independently, is H, C<sub>3-6</sub>-cycloalkyl, C<sub>3-6</sub>-cycloalkyl-C<sub>1-4</sub>-alkyl, aryl-C<sub>1-4</sub>-alkyl or C<sub>1-4</sub>-alkyl optionally substituted on the terminal carbon atom by OH; each of R<sub>5</sub> and R<sub>6</sub>, independently, is H, halogen, C<sub>1-4</sub>-alkyl, CF<sub>3</sub>, OH, SH, NH<sub>2</sub>, C<sub>1-4</sub>-alkoxy, C<sub>1-4</sub>-alkylthio, NHC<sub>1-4</sub>-alkyl, N(C<sub>1-4</sub>-alkyl)<sub>2</sub> or CN; and ring A is optionally substituted; or a salt thereof, as well as a process for the preparation of such compounds, and pharmaceutical compositions comprising such a compound in free form or pharmaceutically-acceptable salt form with a pharmaceutically-acceptable diluent or carrier therefor.

United States Patent 7,358,253B2 (Evenou *et al.*), a continuation of U.S. Application 10/510,027, the National Stage entry of International Application PCT/EP03/03470, published as WO03/082859A1, is directed to a method for treating acute or chronic rejection of organ or tissue allo- or xenografts or graft-versus-host disease in a subject in need of such treatment comprising administering, e.g., by a topical route to the skin or eye, to such subject an effective amount of a compound of the formula



, wherein R<sub>a</sub> is H, CH<sub>3</sub>, CH<sub>2</sub>-CH<sub>3</sub>, or iso-propyl; R<sub>b</sub> is H,

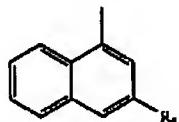
halogen, C<sub>1-6</sub>-alkoxy, or C<sub>1-6</sub>-alkyl, and either R is a radical of the formula



, where R<sub>1</sub> is piperazin-1-yl optionally

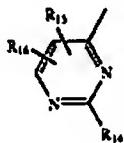
substituted by CH<sub>3</sub> in position 3 or 4, or 4,7-diaza-spiro [2.5] oct-7-yl; R<sub>2</sub> is Cl, Br, CF<sub>3</sub>, or CH<sub>3</sub>; and R<sub>3</sub> is H, CH<sub>3</sub>, or CF<sub>3</sub>, such that R<sub>2</sub> is other than CH<sub>3</sub> or Cl when R<sub>3</sub> is H, R<sub>a</sub> is H or CH<sub>3</sub>, R<sub>b</sub> is H and R<sub>1</sub> is 4-methyl-1-piperazinyl; or a radical of the

(1b)



formula , where R<sub>4</sub> is piperazin-1-yl substituted in position(s) 3 and/or 4 by CH<sub>3</sub>; or 4,7-diaza-spiro[2.5]oct-7-yl, such that R<sub>a</sub> is other than H or CH<sub>3</sub> when R<sub>4</sub> is 4-methyl-1-piperazinyl; or a radical of the formula

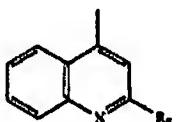
(1c)



, where R<sub>14</sub> is 4,7-diaza-spiro[2.5]oct-7-yl; R<sub>15</sub> is

halogen, CF<sub>3</sub> or CH<sub>3</sub>, such that R<sub>15</sub> is other than CH<sub>3</sub> when R<sub>16</sub> is CH<sub>3</sub>, R<sub>a</sub> is H or CH<sub>3</sub>, and R<sub>b</sub> is H; and R<sub>16</sub> is H, CH<sub>3</sub>, CH<sub>2</sub>-CH<sub>3</sub>, or CF<sub>3</sub>, such that R<sub>16</sub> is other than H when R<sub>15</sub> is Cl, R<sub>a</sub> is H or CH<sub>3</sub>, and R<sub>b</sub> is H; or a radical of the formula

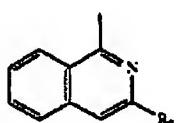
(1d)



, where R<sub>8</sub> is 1-piperazinyl, 3-methyl-piperazin-1-

yl or 4-benzyl-piperazin-1-yl; or a radical of the formula

(1e)



, where R<sub>9</sub> is 4,7-diaza-spiro[2.5]oct-7-yl or 1-

piperazinyl substituted in position 3 by methyl or ethyl or optionally in position 4 by methyl; or a pharmaceutically-acceptable salt thereof, optionally concomitantly or in

sequence with second drug substance selected from immunosuppressant, immunomodulatory, anti-inflammatory, anti-proliferative and anti-diabetic drugs, as well as pharmaceutical compositions comprising such a compound in free form or pharmaceutically-acceptable salt form with a pharmaceutically-acceptable diluent or carrier therefor.

As the compounds of the Published U.S. Application of the parent of the Albert *et al* '774 Patent as well as the compounds of the Published International Application parent of the Evenou *et al* '253 Patent have been discussed and distinguished from the compounds of the instant Application above, and no combination of the two references makes Applicants' compounds any more obvious than either of the references alone, reconsideration and withdrawal of the rejection is respectfully requested.

## SUMMARY

In view of Applicants' amendments and arguments, they respectfully believe that all non-withdrawn pending Claims are now in condition for allowance and earnestly solicit such favorable action of the Examiner, with an early Notice of Allowance being issued. If any remaining matters need to be resolved, however, Applicants respectfully request another telephone interview (the undersigned attorney may be contacted at the telephone number set forth below) with the Examiner prior to any adverse action being issued by the Office in response to these arguments, in order to facilitate allowance of the pending Claims.

Respectfully submitted,

Dated: May 18, 2009

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